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DATE: Wednesday, December 11, 2002

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DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L4	L3 same proteom$	15	L4
L3	L2 same diagnos$	290	L3
L2	L1 same database	7968	L2
L1	peptide or protein	327367	L1

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☐ 1. Document ID: US 20020177242 A1

L4: Entry 1 of 15 File: PGPB Nov 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020177242
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020177242 A1

TITLE: Retentate chromatography and protein chip arrays with applications in biology and medicine

PUBLICATION-DATE: November 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hutchens, T. William	Mountain View	CA	US	
Yip, Tai-Tung	Cupertino	CA	US	

US-CL-CURRENT: 436/518; 435/5, 435/6, 435/7.2, 702/19

ABSTRACT:

This invention provides methods of retentate chromatography for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biology and medicine, including clinical diagnostics and drug discovery.

L4: Entry 1 of 15 File: PGPB Nov 28, 2002

DOCUMENT-IDENTIFIER: US 20020177242 A1
TITLE: Retentate chromatography and protein chip arrays with applications in biology and medicine

Summary of Invention Paragraph (7):
[0006] One goal of functional genomics ("proteomics") is the identification and characterization of organic biomolecules that are differentially expressed between cell types. By comparing expression one can identify molecules that may be responsible for a particular pathologic activity of a cell. For example, identifying a protein that is expressed in cancer cells but not in normal cells is useful for diagnosis and, ultimately, for drug discovery and treatment of the pathology. Upon completion of the Human Genome Project, all the human genes will have been cloned, sequenced and organized in databases. In this "post-genome" world, the ability to identify differentially expressed proteins will lead, in turn, to the identification of the genes that encode them. Thus, the power of genetics can be brought to bear on problems of cell function.

☐ 2. Document ID: US 20020160420 A1

L4: Entry 2 of 15 File: PGPB Oct 31, 2002

PGPUB-DOCUMENT-NUMBER: 20020160420
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020160420 A1

TITLE: Process for diagnosis of physiological conditions by characterization of proteomic materials

PUBLICATION-DATE: October 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Jackowski, George	Kettleby		CA	
Thatcher, Brad	Toronto		CA	
Marshall, John	Toronto		CA	
Yantha, Jason	Toronto		CA	
Vrees, Tammy	Oakville		CA	

US-CL-CURRENT: 435/7.1; 435/7.5, 436/518, 702/19

ABSTRACT:

The present invention discloses the use of proteomic investigation as a diagnostic tool; and particularly teaches the use of proteomic investigative techniques and methodology to determine a proteomic basis for the development and progression of abnormal physiological conditions and the development and characterization of risk assessment, diagnostic and therapeutic means and methodologies.

L4: Entry 2 of 15 File: PGPB Oct 31, 2002

DOCUMENT-IDENTIFIER: US 20020160420 A1
TITLE: Process for diagnosis of physiological conditions by characterization of proteomic materials

Summary of Invention Paragraph (47):
[0044] U.S. Pat. No. 5,538,897 teaches a method for correlating a peptide fragment mass spectrum with amino acid sequences derived from a database. A peptide is analyzed by a tandem mass spectrometer to yield a peptide fragment mass spectrum. A protein sequence database or a nucleotide sequence database is used to predict one or more fragment spectra for comparison with the experimentally derived fragment spectrum. In one embodiment, sub-sequences of the sequences found on the database which define a peptide having a mass substantially equal to the mass of the peptide analyzed by the tandem mass spectrometer are identified as candidate sequences. For each candidate sequence, a plurality of fragments of the sequence are identified and the masses and m/z ratios of the fragments are predicted and used to form a predicted mass spectrum. The various predicted mass spectra are compared to the experimentally derived fragment spectrum using a closeness-of-fit measure, preferably calculated with a two-step process, including a calculation of a preliminary score and, for the highest-scoring predicted spectra, calculation of a correlation function. While useful to determine the source of a particular fragment, the method fails to teach or suggest a means for diagnosing a physiological condition by characterization of proteomic materials.

☐ 3. Document ID: US 20020155509 A1

L4: Entry 3 of 15 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020155509
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020155509 A1

TITLE: Retentate chromatography and protein chip arrays with applications in biology

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Hutchens, T. William	Mountain View	CA	US	
Yip, Tai-Tung	Cupertino	CA	US	

US-CL-CURRENT: 435/7.9

ABSTRACT:

This invention provides methods of retentate chromatography for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biology and medicine, including clinical diagnostics and drug discovery.

L4: Entry 3 of 15 File: PGPB Oct 24, 2002

DOCUMENT-IDENTIFIER: US 20020155509 A1
TITLE: Retentate chromatography and protein chip arrays with applications in biology

Summary of Invention Paragraph (7):
[0006] One goal of functional genomics ("proteomics") is the identification and characterization of organic biomolecules that are differentially expressed between cell types. By comparing expression one can identify molecules that may be responsible for a particular pathologic activity of a cell. For example, identifying a protein that is expressed in cancer cells but not in normal cells is useful for diagnosis and, ultimately, for drug discovery and treatment of the pathology. Upon completion of the Human Genome Project, all the human genes will have been cloned, sequenced and organized in databases. In this "post-genome" world, the ability to identify differentially expressed proteins will lead, in turn, to the identification of the genes that encode them. Thus, the power of genetics can be brought to bear on problems of cell function.

☐ 4. Document ID: US 20020153252 A1

L4: Entry 4 of 15 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020153252
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020153252 A1

TITLE: Multi-dimensional proteomic analysis method

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Akins, Robert E. JR.	Newark	DE	US	

US-CL-CURRENT: 204/459; 204/456, 204/462, 204/466, 204/606, 204/610, 204/613, 204/616

ABSTRACT:

A multi-dimensional proteomic analysis method utilizing cationic electrophoresis is described. The method includes separating proteins in one direction using cationic electrophoresis and separating the proteins in a second orthogonal direction using other electrophoresis separation methods such as denaturing electrophoresis and electrophoresis subsequent to proteolytic cleavage or isofocussing. The two dimensional array may be used to determine various protein-protein interactions in a sample.

L4: Entry 4 of 15 File: PGPB Oct 24, 2002

DOCUMENT-IDENTIFIER: US 20020153252 A1
TITLE: Multi-dimensional proteomic analysis method

Detail Description Paragraph (27):
[0037] A further example of the application of the two dimensional electrophoresis method would be the generation of databases associating the distribution of proteins in two dimensional electrophoretograms to the presence or absence of specific clinical symptoms, syndromes, or diseases. By incorporating the CAT electrophoresis separation method as one of the dimensions in a two-dimensional proteomic analysis, data regarding the interaction of proteins into complexes can be related to specific disease states. In this way, the present invention can be adapted to drug development, diagnostic, and research applications.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 20020142343 A1

L4: Entry 5 of 15 File: PGPB Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020142343
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020142343 A1

TITLE: Retentate chromatography and protein chip arrays with applications in biology

PUBLICATION-DATE: October 3, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Hutchens, T. William	Mountain View	CA	US	
Yip, Tai-Tung	Cupertino	CA	US	

US-CL-CURRENT: 435/6; 427/2.11, 435/7.9

ABSTRACT:

This invention provides methods of retentate chromatography for resolving analytes

in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biology and medicine, including clinical diagnostics and drug discovery.

L4: Entry 5 of 15 File: PGPB Oct 3, 2002

DOCUMENT-IDENTIFIER: US 20020142343 A1
TITLE: Retentate chromatography and protein chip arrays with applications in biology

Summary of Invention Paragraph (7):
[0006] One goal of functional genomics ("proteomics") is the identification and characterization of organic biomolecules that are differentially expressed between cell types. By comparing expression one can identify molecules that may be responsible for a particular pathologic activity of a cell. For example, identifying a protein that is expressed in cancer cells but not in normal cells is useful for diagnosis and, ultimately, for drug discovery and treatment of the pathology. Upon completion of the Human Genome Project, all the human genes will have been cloned, sequenced and organized in databases. In this "post-genome" world, the ability to identify differentially expressed proteins will lead, in turn, to the identification of the genes that encode them. Thus, the power of genetics can be brought to bear on problems of cell function.

☐ 6. Document ID: US 20020127623 A1

L4: Entry 6 of 15 File: PGPB Sep 12, 2002

PGPUB-DOCUMENT-NUMBER: 20020127623
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020127623 A1

TITLE: Biosensors, reagents and diagnostic applications of directed evolution

PUBLICATION-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Minshull, Jeremy	Menlo Park	CA	US	
Davis, S. Christopher	San Francisco	CA	US	
Welch, Mark	Fremont	CA	US	
Raillard, Sun Ai	Mountain View	CA	US	
Vogel, Kurt	Palo Alto	CA	US	
Krebber, Claus	Mountain View	CA	US	

US-CL-CURRENT: 435/7.92; 435/7.1

ABSTRACT:

Methods for sensing test stimuli using arrays of biopolymers are provided. Libraries of biopolymers, such nucleic acid variants, and expression products encoded by nucleic acid variants are provided. Reusable library arrays, and methods for their use are provided.

L4: Entry 6 of 15 File: PGPB Sep 12, 2002

DOCUMENT-IDENTIFIER: US 20020127623 A1
TITLE: Biosensors, reagents and diagnostic applications of directed evolution

Detail Description Paragraph (255):
[0294] Rohlff (2000) "Proteomics in molecular medicine: applications in central nervous systems disorders." Electrophoresis (2000) April 21(6):1227-34 describe proteomics appraoches relevant to CNS disorders. For example, bodily fluids such as cerebrospinal fluid (CSF) and serum are analysed at the time of presentation and throughout the course of the disease. Changes in the protein composition of CSF are indicative of altered CNS protein expression pattern with a causative or diagnostic disease link. Isolation strategies of clinically relevant cellular material such as laser capture micro-dissection, protein enrichment procedures and proteomic approaches to neuropeptide and neurotransmitter analysis are used to map out complex cellular interaction at a high level of detail. The resulting proteome database bypasses ambiguities of experimental models and facilitates pre- and clinical development of more specific disease markers and new selective fast acting therapeutics. Similarly, the present invention uses shuffled components to provide proteomic analysis. In another approach, de Lange (2000) "Detection of complement factor B in the cerebrospinal fluid of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy disease using two-dimensional gel electrophoresis and mass spectrometry. Neurosci Lett 282(3): 149-52 investigated cerebrospinal fluid (CSF) from three CADASIL cases with known mutations in Notch-3 using two-dimensional gel electrophoresis. CSF from these patients was compared to that of six controls. A single spot in the protein maps of patients which was absent from all the controls was observed. In-gel tryptic digestion of this protein followed by mass spectrometric analysis of the tryptic fragments and a database search identified the spot as human complement factor B. In an approach of the present invention, similar approaches are used with shuffled components.

☐ 7. Document ID: US 20020123043 A1

L4: Entry 7 of 15 File: PGPB Sep 5, 2002

PGPUB-DOCUMENT-NUMBER: 20020123043
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020123043 A1

TITLE: RETENTATE CHROMATOGRAPHY AND PROTEIN CHIP ARRAYS WITH APPLICATIONS IN BIOLOGY AND MEDICINE

PUBLICATION-DATE: September 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
HUTCHENS, T. WILLIAM	LOS ALTOS	CA	US	
YIP, TAI-TUNG	CUPERTINO	CA	US	

US-CL-CURRENT: 435/6

ABSTRACT:

This invention provides methods of retentate chromatography for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biology and medicine, including clinical diagnostics and drug discovery.

L4: Entry 7 of 15 File: PGPB Sep 5, 2002

DOCUMENT-IDENTIFIER: US 20020123043 A1
TITLE: RETENTATE CHROMATOGRAPHY AND PROTEIN CHIP ARRAYS WITH APPLICATIONS IN BIOLOGY AND MEDICINE

Summary of Invention Paragraph (7):
[0006] One goal of functional genomics ("proteomics") is the identification and characterization of organic biomolecules that are differentially expressed between cell types. By comparing expression one can identify molecules that may be responsible for a particular pathologic activity of a cell. For example, identifying a protein that is expressed in cancer cells but not in normal cells is useful for diagnosis and, ultimately, for drug discovery and treatment of the pathology. Upon completion of the Human Genome Project, all the human genes will have been cloned, sequenced and organized in databases. In this "post-genome" world, the ability to identify differentially expressed proteins will lead, in turn, to the identification of the genes that encode them. Thus, the power of genetics can be brought to bear on problems of cell function.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments
KWIC | Draw Desc | Image

☐ 8. Document ID: US 20020102568 A1

L4: Entry 8 of 15 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020102568
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020102568 A1

TITLE: Nucleic acid sensor molecules

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Usman, Nassim	Lafayette	CO	US	
McSwiggen, James A.	Boulder	CO	US	
Zinnen, Shawn	Denver	CO	US	
Seiwert, Scott	Lyons	CO	US	
Haeberli, Peter	Berthoud	CO	US	
Chowrira, Bharat	Broomfield	CO	US	
Blatt, Lawrence	Boulder	CO	US	
Vaish, Narendra K.	Boulder	CO	US	

US-CL-CURRENT: 435/6; 536/24.3

ABSTRACT:

Nucleic acid sensor molecules and methods are disclosed for the detection and amplification of signaling agents using enzymatic nucleic acid constructs, including hammerhead enzymatic nucleic acid molecules, inozymes, G-cleaver enzymatic nucleic acid molecules, zinzymes, amberzymes and DNAzymes; kits for detection and amplification; use in diagnostics, nucleic acid circuits, nucleic acid computers, therapeutics, target validation, target discovery, drug optimization, SNP detection, SNP scoring, proteome scoring and other uses are disclosed.

DOCUMENT-IDENTIFIER: US 20020102568 A1
TITLE: Nucleic acid sensor molecules

Summary of Invention Paragraph (188):
[0183] In another embodiment, the nucleic acid sensor molecules (allozymes) are used to detect the presence of or absence peptides and/or proteins in a system, for example in a blood sample, cell extract, cell, or entire organism. These nucleic acid molecules can be used in place of Elisa or Western Blot analysis, and provide a broader array of criteria to differentiate proteins and peptides in vivo. The nucleic acid sensor molecules can be used to differentiate proteins or peptides that differ in sequence, conformation, activation state or phosphorylation state, or by other post-translational modifications. An array of nucleic acid sensor molecules, for example when attached to a surface such as a chip or bead, can be used to detect and profile peptides and/or proteins in a system. As such, nucleic acid sensor molecules can be used in proteome discovery, detection, and scoring. In a non-limiting example, a plurality of nucleic acid sensor molecule is used to screen a fetus, infant, child or adult's proteome. A sample of genetic material is obtained from, for example amniotic fluid, chorionic villus, blood, or hair and is contacted with an array of nucleic acid sensor molecules. The array of nucleic acid sensor molecules comprises a proteome library such that the presence of any predetermined peptide or protein is indicated by the corresponding nucleic acid sensor by measuring the extent of the signal produced when the nucleic acid sensor interacts with the peptide or protein, for example by measuring fluorescence, color change, precipitate deposition, voltage or current. For example, a nucleic acid computer device of the invention can be integrated into the nucleic acid sensor array such that the output of the array is recorded electronically and can be subsequently downloaded into a database. The information generated by the nucleic acid sensor array can be used in diagnostic molecular profiling applications such as protein mapping or profiling for various purposes, for example in target discovery, target validation, drug discovery, determining susceptibility to disease, determining the potential effect of various treatments or therapies, predicting drug metabolism or drug response, selecting candidates for clinical trials, and for managing the treatment of disease in individual patients.

☐ 9. Document ID: US 20020087273 A1

L4: Entry 9 of 15 File: PGPB Jul 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020087273
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020087273 A1

TITLE: Reference database

PUBLICATION-DATE: July 4, 2002

INVENTOR-INFORMATION: NAME	CITY	STATE	COUNTRY	RULE-47
Anderson, Norman G.	Rockville	MD	US	
Anderson, N. Leigh	Washington	DC	US	

US-CL-CURRENT: 702/19; 530/350

ABSTRACT:

Data acquisition and cataloging are used to classify polypeptides into a reference index or database. The database can be used to identify previously unidentified samples. New polypeptides are characterized and added to the database.

L4: Entry 9 of 15 File: PGPB Jul 4, 2002

DOCUMENT-IDENTIFIER: US 20020087273 A1
TITLE: Reference database

Detail Description Paragraph (229):
[0251] The proteomics database (e.g.,the apparatus 100 in FIG. 7) is useful for comparing markers and targets, as well as for creating microarray chips having tissue markers or antibodies for use as tissue-specific diagnostic tools. In addition, the proteomics database of the present invention can be used to compare samples from a treated patient with a protein index corresponding to normal samples to determine effectiveness of a therapy or biological effect of a candidate therapy. Thus, identifying which proteins have changed provides information regarding how proteins work and response to the treatment.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 10. Document ID: US 20020069208 A1

L4: Entry 10 of 15 File: PGPB Jun 6, 2002

PGPUB-DOCUMENT-NUMBER: 20020069208
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020069208 A1

TITLE: Method of and system for generating data-base compilation and storage, accessing, comparing and analyzing of scanned genetic spot pattern images and the like

PUBLICATION-DATE: June 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rines, R. David	San Antonio	TX	US	

US-CL-CURRENT: 707/104.1

ABSTRACT:

A new method of and system for generating, storing and accessing genomic information provided in the format of spot pattern images of electrophoretically separated gene fragments and the like to derive from appropriately customized assay kits, using standardized formats of such spot pattern images for storage in an image database library, and with preferably internet two-way communication between remote research or diagnostic customers or users and the central data base library for permitting customers remote inputting of spot pattern images for growing the data base and/or for analysis, customer retrieval of stored data base library images, and for communicating image comparison and analysis services from the database library to the customers or users--such constituting also a new method of doing business in this field.

L4: Entry 10 of 15 File: PGPB Jun 6, 2002

DOCUMENT-IDENTIFIER: US 20020069208 A1

TITLE: Method of and system for generating data-base compilation and storage, accessing, comparing and analyzing of scanned genetic spot pattern images and the like

Summary of Invention Paragraph (10):
[0008] In exchange for the submission of gene/individual specific TDGS spot patterns and associated phenotypic (trait/characteristics) data to the database, researchers can now gain access to research results obtained by TDGS based research worldwide. This approach will facilitate the generation of statistically significant findings on a global scale. Further, mating the database to existing genomic and proteomic tools (for example protein modeling software/resources and existing and emerging genetic variant databases) provides the opportunity for researchers to rapidly establish functional significance of their findings. The establishment of the spot pattern database system will provide researchers with the opportunity to conduct studies of unprecedented scope that can be immediately compared to data gathered from studies occurring worldwide, dramatically enhancing the appeal of the technology platform. Further, effective mining of the database will allow the validation of diagnostic services and the identification of suitable target populations. The development of such a database library of core spot pattern images, moreover, provides opportunities to mine the collected data and assemble marker systems of high diagnostic and commercial utility for a variety of industries that are coupled to the use of TDGS assays. Because the database (currently referred to as the Origin Diversity.TM. Database) will be compiled from multi-gene research from populations all over the world, this spot pattern database may be the first of its kind, allowing the Scientific/Medical community directly to address issues of multi-gene involvement in the predisposition, onset and treatment of many diseases at both the research and diagnostic testing levels

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☐ 11. Document ID: US 20020055186 A1

L4: Entry 11 of 15 File: PGPB May 9, 2002

PGPUB-DOCUMENT-NUMBER: 20020055186
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020055186 A1

TITLE: Detection of peptides

PUBLICATION-DATE: May 9, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Barry, Richard	Abingdon		GB	
Platt, Albert Edward	Abingdon		GB	
Scrivener, Elaine	Abingdon		GB	
Soloviev, Mikhail	Abingdon		GB	
Terrett, Jonathan Alexander	Abingdon		GB	

US-CL-CURRENT: 436/518

ABSTRACT:

The present invention provides a method and devices for determining the presence of proteins of interest in a sample. In practice, the method comprises submitting the sample to conditions that allow fragmentation of the proteins into target peptide fragments. The target peptide fragments are then contacted with an array of capture agents, such as antibodies, immobilized on a solid support. The capture agents

recognize a target peptide fragment of a protein of interest. Binding of a target peptide fragment with an antibody is indicative of the presence of a protein of interest in the sample. The invention further provides a method for producing an array for capturing a target peptide fragment of a protein of interest, which comprises immobilizing capture agents on a solid support, wherein each capture agent specifically recognizes a sequence of a region of a target peptide fragment from a different protein of interest. The methods and arrays (devices) of the invention provide for proteomics, diagnosis, pharmacoproteomics, identification of markers of disease, and drug target discovery. The methods and arrays are particularly suitable for generating a database of information relating to protein expression.

L4: Entry 11 of 15 File: PGPB May 9, 2002

DOCUMENT-IDENTIFIER: US 20020055186 A1
TITLE: Detection of peptides

Abstract Paragraph (1):
The present invention provides a method and devices for determining the presence of proteins of interest in a sample. In practice, the method comprises submitting the sample to conditions that allow fragmentation of the proteins into target peptide fragments. The target peptide fragments are then contacted with an array of capture agents, such as antibodies, immobilized on a solid support. The capture agents recognize a target peptide fragment of a protein of interest. Binding of a target peptide fragment with an antibody is indicative of the presence of a protein of interest in the sample. The invention further provides a method for producing an array for capturing a target peptide fragment of a protein of interest, which comprises immobilizing capture agents on a solid support, wherein each capture agent specifically recognizes a sequence of a region of a target peptide fragment from a different protein of interest. The methods and arrays (devices) of the invention provide for proteomics, diagnosis, pharmacoproteomics, identification of markers of disease, and drug target discovery. The methods and arrays are particularly suitable for generating a database of information relating to protein expression.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 12. Document ID: US 20020046054 A1

L4: Entry 12 of 15 File: PGPB Apr 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020046054
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020046054 A1

TITLE: Use of blood and plasma donor samples and data in the drug discovery process

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Morand, Patrick G.	Northbrook	IL	US	
Ostro, Marc J.	Pennington	NJ	US	

US-CL-CURRENT: 705/1; 700/1

ABSTRACT:

Systems consistent with the present invention provide a method for identifying and recruiting donors whose demographic characteristics, genomic and proteomic profile,

and medical histories make them attractive candidates for clinical trials, drug target identification, and pharmacogenomic studies.

L4: Entry 12 of 15 File: PGPB Apr 18, 2002

DOCUMENT-IDENTIFIER: US 20020046054 A1
TITLE: Use of blood and plasma donor samples and data in the drug discovery process

Detail Description Paragraph (51):
[0073] An example of information that may be stored in the proteomic/genomics database is shown in FIG. 3. Assays performed on samples 301 and 311, which are collected from the same individual at different times, show a DNA polymorphism (e.g., a SNP), but show normal RNA and protein expression. At the times samples 301 and 311 are collected, the individual shows no sign of disease. Assays performed on samples 321 and 331, again collected from this individual but at later times, as before show a DNA polymorphism and now also show abnormal expression of at least one protein and/or RNA. The amount of abnormal expression increases between the date sample 321 is collected and the date sample 331 is collected. At the time sample 341 is collected, the individual has begun to show disease symptoms. The DNA polymorphism persists and the extent of abnormal protein/RNA expression has increased. The DNA polymorphism persists in sample 351, but the abnormal protein and/or RNA is more or less abundant. Disease severity has worsened at the time sample 351 is collected, suggesting that the DNA polymorphism and the expression abnormality may be diagnostic for the disease and may be therapeutic targets.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 13. Document ID: US 20010014461 A1

L4: Entry 13 of 15 File: PGPB Aug 16, 2001

PGPUB-DOCUMENT-NUMBER: 20010014461
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010014461 A1

TITLE: Retentate chromatography and protein chip arrays with applications in biology and medicine

PUBLICATION-DATE: August 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hutchens, T. William	Los Altos	CA	US	
Yip, Tai-Tung	Cupertino	CA	US	

US-CL-CURRENT: 435/7.92

ABSTRACT:

This invention provides methods of retentate chromatography for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biology and medicine, including clinical diagnostics and drug discovery.

L4: Entry 13 of 15 File: PGPB Aug 16, 2001

DOCUMENT-IDENTIFIER: US 20010014461 A1

TITLE: Retentate chromatography and protein chip arrays with applications in biology and medicine

Summary of Invention Paragraph (8):
[0007] One goal of functional genomics ("proteomics") is the identification and characterization of organic biomolecules that are differentially expressed between cell types. By comparing expression one can identify molecules that may be responsible for a particular pathologic activity of a cell. For example, identifying a protein that is expressed in cancer cells but not in normal cells is useful for diagnosis and, ultimately, for drug discovery and treatment of the pathology. Upon completion of the Human Genome Project, all the human genes will have been cloned, sequenced and organized in databases. In this "post-genome" world, the ability to identify differentially expressed proteins will lead, in turn, to the identification of the genes that encode them. Thus, the power of genetics can be brought to bear on problems of cell function.

☐ 14. Document ID: US 6225047 B1

L4: Entry 14 of 15 File: USPT May 1, 2001

US-PAT-NO: 6225047
DOCUMENT-IDENTIFIER: US 6225047 B1

TITLE: Use of retentate chromatography to generate difference maps

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:				
NAME	CITY	STATE	ZIP CODE	COUNTRY
Hutchens; T. William	Los Altos	CA		
Yip; Tai-Tung	Cupertino	CA		

US-CL-CURRENT: 435/5; 210/656, 422/59, 422/70, 435/174, 435/177, 435/182, 435/288.6, 435/7.2, 435/7.21, 435/7.22, 435/7.32, 436/161, 436/514, 436/518, 436/541, 436/824, 530/412, 530/413, 530/415, 530/417

ABSTRACT:

This is invention is directed to methods of identifying analytes that are differentially present between two samples. The methods involve determining retention data by desorption spectrometry for analytes in different samples using the same selectivity conditions, comparing the data, and identifying analytes that are differentially retained.

22 Claims, 48 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 44

L4: Entry 14 of 15 File: USPT May 1, 2001

DOCUMENT-IDENTIFIER: US 6225047 B1
TITLE: Use of retentate chromatography to generate difference maps

Brief Summary Text (7):
One goal of functional genomics ("proteomics") is the identification and

characterization of organic biomolecules that are differentially expressed between cell types. By comparing expression one can identify molecules that may be responsible for a particular pathologic activity of a cell. For example, identifying a protein that is expressed in cancer cells but not in normal cells is useful for diagnosis and, ultimately, for drug discovery and treatment of the pathology. Upon completion of the Human Genome Project, all the human genes will have been cloned, sequenced and organized in databases. In this "post-genome" world, the ability to identify differentially expressed proteins will lead, in turn, to the identification of the genes that encode them. Thus, the power of genetics can be brought to bear on problems of cell function.

☐ 15. Document ID: WO 102848 A1

L4: Entry 15 of 15 File: EPAB Jan 11, 2001

PUB-NO: WO0000102848A1
DOCUMENT-IDENTIFIER: WO 102848 A1
TITLE: METHOD FOR THE MULTI-DIMENSIONAL ANALYSIS OF A PROTEOME

PUBN-DATE: January 11, 2001

INVENTOR-INFORMATION:	
NAME	COUNTRY
MOORE, THOMAS	DE
HORN, ANTON	DE
KREUSCH, STEFAN	DE

INT-CL (IPC): G01 N 30/46
EUR-CL (EPC): G01N033/68

ABSTRACT:

CHG DATE=20010202 STATUS=O>The invention relates to a method for the multi-dimensional analysis of a proteome. The method is used in the biochemical, biotechnological and medical fields and in the pharmaceutical industry for diagnostic purposes and for developing biologically active substances. The aim of the invention is to improve, facilitate and for certain proteins first of all to enable the quantification and identification of the proteins of a proteome. According to the invention, the proteins of a proteome are subjected to a large number n of different separation processes under standardised conditions in such a way, that each respective liquid fraction m1, obtained in a separation stage, delivers m2 liquid fractions in a separation stage which immediately follows. After n separation stages, m1* m2* ....mn = M liquid fractions have been produced which are identified qualitatively or quantitatively by known identification methods using o different analysis methods and which are quantitatively determined also by known quantification methods in such a way, that once the analysis data has been unified in a database, an n-dimensional image of the proteome is obtained which is characterised by identifiers and quantifiers and by the position in the n-dimensional network.

L4: Entry 15 of 15 File: EPAB Jan 11, 2001

DOCUMENT-IDENTIFIER: WO 102848 A1
TITLE: METHOD FOR THE MULTI-DIMENSIONAL ANALYSIS OF A PROTEOME

Abstract (1):

CHG DATE=20010202 STATUS=O>The invention relates to a method for the multi-dimensional analysis of a proteome. The method is used in the biochemical, biotechnological and medical fields and in the pharmaceutical industry for diagnostic purposes and for developing biologically active substances. The aim of the invention is to improve, facilitate and for certain proteins first of all to enable the quantification and identification of the proteins of a proteome. According to the invention, the proteins of a proteome are subjected to a large number n of different separation processes under standardised conditions in such a way, that each respective liquid fraction m1, obtained in a separation stage, delivers m2 liquid fractions in a separation stage which immediately follows. After n separation stages, m1* m2* ....mn = M liquid fractions have been produced which are identified qualitatively or quantitatively by known identification methods using o different analysis methods and which are quantitatively determined also by known quantification methods in such a way, that once the analysis data has been unified in a database, an n-dimensional image of the proteome is obtained which is characterised by identifiers and quantifiers and by the position in the n-dimensional network.

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PROTEOMACULANS.DWPI,EPAB,JPAB,USPT,PGPB.	4
PROTEOMANALYSIS.DWPI,EPAB,JPAB,USPT,PGPB.	1
PROTEOME.DWPI,EPAB,JPAB,USPT,PGPB.	356
PROTEOMES.DWPI,EPAB,JPAB,USPT,PGPB.	62
PROTEOMES-SECING.DWPI,EPAB,JPAB,USPT,PGPB.	1
PROTEOMES:.DWPI,EPAB,JPAB,USPT,PGPB.	1
PROTEOMETABOLISM.DWPI,EPAB,JPAB,USPT,PGPB.	1
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(L3 SAME PROTEOM$).USPT,PGPB,JPAB,EPAB,DWPI.	15

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NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded
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L6 ANSWER 1 OF 30 MEDLINE
AN 2000246567 MEDLINE
DN 20246567 PubMed ID: 10786895
TI Proteomics in molecular medicine: applications in central nervous systems disorders.
AU Rohlff C
CS Oxford GlycoSciences, Abingdon Science Park, United Kingdom.. christian.rohlff@ogs.co.uk
SO ELECTROPHORESIS, **(2000 Apr)** 21 (6) 1227-34. Ref: 112
Journal code: 8204476. ISSN: 0173-0835.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200006
ED Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000628
AB Bodily fluids such as cerebrospinal fluid (CSF) and serum can be analysed at the time of presentation and throughout the course of the disease. Changes in the **protein** composition of CSF may be indicative of

altered CNS **protein** expression pattern with a causative or **diagnostic** disease link. These findings can be strengthened through subsequent proteomic analysis of specific brain areas implicated in the pathology. New isolation strategies of clinically relevant cellular material such as laser capture microdissection, **protein** enrichment procedures and proteomic approaches to neuropeptide and neurotransmitter analysis give us the opportunity to map out complex cellular interaction at an unprecedented level of detail. In neurological disorders multiple underlying pathogenic mechanisms as well as an acute and a chronic CNS disease components may require a selective repertoire of molecular targets and biomarkers rather than an individual **protein** to better define a complex disease. The resulting proteome **database** bypasses many ambiguities of experimental models and may facilitate pre- and clinical development of more specific disease markers and new selective fast acting therapeutics.

L6 ANSWER 2 OF 30 MEDLINE
AN 2000246565 MEDLINE
DN 20246565 PubMed ID: 10786893
TI Cancer proteomics: from identification of novel markers to creation of artifical learning models for tumor classification.
AU Alaiya A A; Franzen B; Auer G; Linder S
CS Unit of Cancer Proteomics, Karolinska Institute and Hospital, Stockholm, Sweden.. ayodele.alaiya@cck.ki.se
SO ELECTROPHORESIS, **(2000 Apr)** 21 (6) 1210-7. Ref: 76
Journal code: 8204476. ISSN: 0173-0835.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200006
ED Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000628
AB Studies of global **protein** expression in human tumors have led to the identification of various polypeptide markers, potentially useful as **diagnostic** tools. Many changes in gene expression recorded between benign and malignant human tumors are due to post-translational modifications, not detected by analyses of RNA. Proteome analyses have also yielded information about tumor heterogeneity and the degree of relatedness between primary tumors and their metastases. Results from our own studies have shown a similar pattern of changes in **protein** expression in different epithelial tumors, such as decreases in tropomyosin and cytokeratin expression and increases in proliferating cell nuclear antigen (PCNA) and heat shock **protein** expression. Such information has been used to create artificial learning models for tumor classification. The artificial learning approach has potential to improve tumor **diagnosis** and cancer treatment prediction.

L6 ANSWER 3 OF 30 MEDLINE
AN 2001066594 MEDLINE
DN 20556510 PubMed ID: 11102317
TI Cell-cycle dysregulation in breast cancer: breast cancer therapies targeting the cell cycle.
AU Zafonte B T; Hulit J; Amanatullah D F; Albanese C; Wang C; Rosen E; Reutens A; Sparano J A; Lisanti M P; Pestell R G
CS Division of Hormone-Dependent Tumor Biology, The Albert Einstein Comprehensive Cancer Center, Department of Development and Molecular Biology, Bronx, New York 10461, USA.
NC CA13330 (NCI)
RO1CA70897 (NCI)
RO1CA75503 (NCI)
+

SO FRONTIERS IN BIOSCIENCE, **(2000 Dec 1)** 5 D938-61. Ref: 271
Journal code: 9702166. ISSN: 1093-4715.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222
AB Breast cancer is the most commonly **diagnosed** cancer in American women. The underlying mechanisms that cause aberrant cell proliferation and tumor growth involve conserved pathways, which include components of the cell cycle machinery. Proto-oncogenes, growth factors, and steroids have been implicated in the pathogenesis of breast cancer. Surgery, local irradiation, and chemotherapy have been the mainstay of treatment for early and advanced stage disease. Potential targets for selective breast cancer therapy are herein reviewed. Improved understanding of the biology of breast cancer has led to more specific "targeted therapies" directed at biological processes that are selectively deregulated in the cancerous cells. Examples include tamoxifen for estrogen receptor positive tumors and imunoneutralizing antibodies such as trastuzumab for Her2/neu overexpressing tumors. Other novel anticancer agents such as paclitaxel, a microtubule binding molecule, and flavopiridol, a cyclin dependent kinase inhibitor, exert their anticancer effects by inhibiting cell cycle progression.

L6 ANSWER 4 OF 30 MEDLINE
AN 2000115160 MEDLINE
DN 20115160 PubMed ID: 10648389
TI Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed.
CM Erratum in: Blood 2000 Apr 15;95(8):2481
AU Thieblemont C; Berger F; Dumontet C; Moullet I; Bouafia F; Felman P; Salles G; Coiffier B
CS Service d'hematologie and laboratoire d'hematologie, Centre Hospitalier Lyon Sud, Pierre-Benite, France.
SO BLOOD, **(2000 Feb 1)** 95 (3) 802-6. Ref: 25
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, MULTICASE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200002
ED Entered STN: 20000309
Last Updated on STN: 20000525
Entered Medline: 20000224
AB Mucosa-associated lymphoid tissue-derived lymphoma (MALT lymphoma) is usually a very indolent lymphoma, described as localized at **diagnosis** and remaining localized for a prolonged period; dissemination occurs only after a long course of evolution. In our **database**, out of 158 patients with MALT lymphoma, 54 patients presented with a disseminated disease at **diagnosis**. Of these 54 patients, 17 patients (30%) presented with multiple involved mucosal sites; 37 patients (70%) presented with 1 involved mucosal site, but in 23 of these patients (44%), dissemination of the disease was due to bone marrow involvement; 12 patients (22%) had multiple lymph node involvement; and 2 patients (4%) had nonmucosal site involvement. No significant difference in clinical characteristics (sex, age, performance status, B symptoms) and biological parameters (hemoglobin [Hb] and lactate dehydrogenase levels) was observed between localized or disseminated

MALT-lymphoma patients. Only beta2-microglobulin level was significantly more elevated in disseminated disease patients than in localized disease patients. Complete response after the first treatment was achieved in 74% of the patients, and there was no difference between the 2 groups. With a median follow-up of 4 years, the estimated 5- and 10-year overall survival rates were similar in the 2 groups, 86% and 80%, respectively. The median freedom-from-progression survival was 5.6 years for all patients, surprisingly without any difference between localized and disseminated MALT-lymphoma patients. In conclusion, MALT lymphoma is an indolent disease but presents as a disseminated disease in one-third of the cases at **diagnosis**. The dissemination does not change the outcome of the patients.

L6 ANSWER 5 OF 30 MEDLINE
AN 2001183320 MEDLINE
DN 20555535 PubMed ID: 11105949
TI Retrospective study of 338 canine oral melanomas with clinical, histologic, and immunohistochemical review of 129 cases.
AU Ramos-Vara J A; Beissenherz M E; Miller M A; Johnson G C; Pace L W; Fard A; Kottler S J
CS Veterinary Medical Diagnostic Laboratory, College of Veterinary Medicine, University of Missouri, Columbia 65205, USA.
SO VETERINARY PATHOLOGY, **(2000 Nov)** 37 (6) 597-608. Ref: 60
Journal code: 0312020. ISSN: 0300-9858.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329
AB **Diagnostic** records from 338 canine oral melanomas in 338 dogs received at the Veterinary Medical **Diagnostic** Laboratory (1992-1999) were reviewed. Of these tumors, 122 plus an additional 7 metastatic melanomas of unknown origin were selected for clinical follow-up, histologic review, and immunohistochemistry. Chow Chow, Golden Retriever, and Pekingese/Poodle mix breeds were overrepresented, whereas Boxer and German Shepherd breeds were underrepresented. There was no gender predisposition and the average age at presentation was 11.4 years. Forty-nine dogs were euthanized due to recurrence or metastasis. The average postsurgical survival time was 173 days. The gingiva and the labial mucosa were the most common sites. Most tumors were composed of either polygonal cells (27 cases, 20.9%), spindle cells (44 cases, 34.1%), or a mixture of the two (polygonal and spindle) (54 cases, 41.9%). Clear cell (3 cases, 2.3%) and adenoid/papillary (1 case, 0.8%) patterns were uncommon. The metastases of 6/6 oral melanomas had morphologic and immunohistochemical features similar to those of the primary tumors. Immunohistochemically, Melan A was detected in 113/122 oral (92.6%) and 5/7 (71.9%) metastatic melanomas. Only 4/163 nonmelanocytic tumors were focally and weakly positive for Melan A. Antibodies against vimentin, S100 **protein**, and neuron-specific enolase stained 129 (100%), 98 (76%), and 115 (89.1%) of 129 melanomas, respectively. Antibodies against other melanocytic-associated antigens (tyrosinase, glycoprotein 100) did not yield adequate staining. We conclude that Melan A is a specific and sensitive marker for canine melanomas.

L6 ANSWER 6 OF 30 MEDLINE
AN 2001065260 MEDLINE
DN 20432911 PubMed ID: 10976392
TI The genetics of spondyloarthropathies.
AU Fong K Y
CS Department of Medicine, National University of Singapore, Singapore..

mdcfky@nus.edu.sg
SO ANNALS OF THE ACADEMY OF MEDICINE, SINGAPORE, **(2000 May)** 29 (3) 370-5. Ref: 68
Journal code: 7503289. ISSN: 0304-4602.
CY Singapore
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001228
AB INTRODUCTION: Spondyloarthropathies are a heterogeneous group of rheumatic disorders that commonly present with axial skeleton or sacroiliac joints involvement. Ocular involvement like uveitis, iritis and conjunctivitis can be present in up to a third of the patients. Genetic factors play a part in the pathogenesis of spondyloarthropathies. Association with the HLA-B27 gene, especially that between ankylosing spondylitis and HLA-B27 antigenic positivity, is one of the strongest association seen between a disease and a Class I antigen. This paper aims to review the frequencies of HLA-B27 gene and its subtypes in different population groups, possible mechanisms leading to the development of joint inflammation and the risk it confers for development of spondyloarthropathies. METHODS: The MEDLINE **database** was searched using keywords: HLA-B27, spondyloarthropathy, molecular mimicry, arthritogenic **peptides**, reactive arthritis and ankylosing arthritis. Related articles for selected papers were also consulted. Books on HLA-B27 and spondyloarthropathy were obtained through the NUS Medical Library's LINC system. RESULTS: The genetic subtypes and susceptibility to development of disease vary in different population groups. Other HLA genes and non-HLA genes also play a part in the development of spondyloarthropathies, especially in those who are HLA-B27 negative. HLA-B27-positive relatives of spondyloarthritics have a higher risk of developing a similar condition. The presence of the HLA-B27 gene may serve as an aid to **diagnosis** or prognosis for clinicians. In juvenile arthritic patients, it is a poor prognostic factor, predicting for disease severity. It is also associated with poor outcomes for patients with anterior uveitis. However screening of asymptomatic individuals for the HLA-B27 gene is not recommended. CONCLUSION: The polygenic nature of the disease needs further elucidation and study.

L6 ANSWER 7 OF 30 MEDLINE
AN 2001065370 MEDLINE
DN 20431420 PubMed ID: 10976908
TI Objective biologic parameters and their clinical relevance in assessing salivary gland neoplasms.
AU Pinto A E; Fonseca I; Martins C; Soares J
CS Departamento de Patologia Morfologica e Centro de Investigacaode Patobiologia Molecular do Instituto Portugues de Oncologia de Francisco Gentil, Centro de Lisboa, Portugal.
SO ADVANCES IN ANATOMIC PATHOLOGY, **(2000 Sep)** 7 (5) 294-306. Ref: 131
Journal code: 9435676. ISSN: 1072-4109.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200012
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222

AB This review summarizes research advances of cytometric, proliferation, cytogenetic, and molecular "objective" measurable parameters, as additional aids to prognostic information of salivary gland tumors provided by classical clinicopathologic indicators. Flow cytometric DNA ploidy and S-phase fraction seem to be of value as predictors of tumor behavior, aneuploidy, and high S-phase identifying an unfavorable clinical evolution of salivary gland neoplasms. Cell proliferation markers assessed by immunohistochemistry (e.g., PCNA, Ki-67) also appear to have predictive significance, but some conflicting results, in part related to technical procedures, limit their routine clinical application. Silver-stained methods (AgNORs) show a scarce value in estimating prognosis of salivary gland malignancies. p53 and c-erbB-2 as well as karyotyping, are of disputable benefit for clinical use, but the biologic information they provide give a better understanding on the molecular mechanisms involved in the development and progression of tumors. Further studies, with large **databases**, long follow-up information, uniformized histologic classification, and standardized methodologies, are needed to establish how these "objective" parameters would be of truly beneficial for the treatment of patients with salivary gland tumors.

L6 ANSWER 8 OF 30 MEDLINE
AN 2000145553 MEDLINE
DN 20145553 PubMed ID: 10679346
TI Biotechnology match making: screening orphan ligands and receptors.
AU Williams C
CS Millennium Pharmaceuticals, Cambridge, MA 02139-4853, USA.
SO CURRENT OPINION IN BIOTECHNOLOGY, **(2000 Feb)** 11 (1) 42-6. Ref: 36
Journal code: 9100492. ISSN: 0958-1669.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000310
AB To date there has been a considerable amount of interest and success in the pharmaceutical industry in the discovery of drug targets and **diagnostics** via genomic technologies, namely DNA sequencing, mutation/polymorphism detection and expression monitoring of mRNA. As the ultimate targets for the majority of these methods are actually **proteins**, more and more emphasis has been placed upon **protein**-based methods in an effort to define the function of **proteins** discovered by genomic technologies. One of the most challenging areas of drug target discovery facing researchers today is the search for novel receptor-ligand pairs. **Database** mining techniques in conjunction with other computational methods are able to identify many novel sequences of putative receptors, but the ability to similarly identify the receptor's natural ligand is not possible by these methods. The past few years have seen an increase in methodology and instrumentation focused on the ability to discover and characterize **protein-protein** interactions, as well as receptor-ligand pairs. Significant advances have been made in the areas of instrumentation (biosensors and fluorescent plate readers) as well as methodologies relating to phage/ribosome display and library construction.

L6 ANSWER 9 OF 30 MEDLINE
AN 2000436353 MEDLINE
DN 20437398 PubMed ID: 10967322
TI Gene expression profiling: monitoring transcription and translation products using DNA microarrays and proteomics.
AU Celis J E; Kruhoffer M; Gromova I; Frederiksen C; Ostergaard M; Thykjaer

T; Gromov P; Yu J; Palsdottir H; Magnusson N; Orntoft T F
CS Department of Medical Biochemistry and Danish Centre for Human Genome Research, University of Aarhus, Denmark.. jec@biokemi.au.dk
SO FEBS LETTERS, **(2000 Aug 25)** 480 (1) 2-16. Ref: 143
Journal code: 0155157. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000921
AB Novel and powerful technologies such as DNA microarrays and proteomics have made possible the analysis of the expression levels of multiple genes simultaneously both in health and disease. In combination, these technologies promise to revolutionize biology, in particular in the area of molecular medicine as they are expected to reveal gene regulation events involved in disease progression as well as to pinpoint potential targets for drug discovery and **diagnostics**. Here, we review the current status of these technologies and highlight some studies in which they have been applied in concert to the analysis of biopsy specimens.

L6 ANSWER 10 OF 30 MEDLINE
AN 1999420863 MEDLINE
DN 99420863 PubMed ID: 10493120
TI **Diagnosis** of cellular states of microbial organisms using proteomics.
AU VanBogelen R A; Schiller E E; Thomas J D; Neidhardt F C
CS Molecular Biology Department, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, MI 48105, USA.. vanbogr@aa.wl.com
SO ELECTROPHORESIS, **(1999 Aug)** 20 (11) 2149-59. Ref: 26
Journal code: 8204476. ISSN: 0173-0835.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991209
AB Two-dimensional (2-D) polyacrylamide gel electrophoresis has much to contribute to experimental analysis of the proteomes of microbial organisms, since this method separates most cellular **proteins** and allows synthesis rates to be determined quantitatively. **Databases** generated using 2-D gels can grow to be very large from even just a few experiments, since each sample provides the data for a field (or column) in the **database** for several hundreds to even thousands of records (or rows), each of which represents a single polypeptide species. The value of such **databases** for generating an encyclopedia of how each of the cell's **proteins** behave in different conditions (**protein** phenotypes) has been recognized for some time. The potential exists, however, to glean even more valuable information from such **databases**. Because the measurements of each **protein** are made in the context of all other **proteins**, a comprehensive glimpse of the cell's physiological state is theoretically achievable with each 2-D gel. By examining enough conditions (and 2-D gels), expression patterns of subsets of **proteins** (proteomic signatures) can be found that correlate with the cell's state. This type of information can provide a unique

contribution to proteomic analysis, and should be a major focus of such analyses.

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L6 ANSWER 11 OF 30 MEDLINE
AN 1999378331 MEDLINE
DN 99378331 PubMed ID: 10451122
TI Proteomics in human disease: cancer, heart and infectious diseases.
AU Jungblut P R; Zimny-Arndt U; Zeindl-Eberhart E; Stulik J; Koupilova K; Pleissner K P; Otto A; Muller E C; Sokolowska-Kohler W; Grabher G; Stoffler G
CS Max-Planck-Institut fur Infektionsbiologie, Protein Analyse Einheit, Berlin, Germany.. jungblut@mpiib-berlin.mpg.de
SO ELECTROPHORESIS, **(1999 Jul)** 20 (10) 2100-10. Ref: 66
Journal code: 8204476. ISSN: 0173-0835.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19990925
Last Updated on STN: 19990925
Entered Medline: 19990910
AB In recent years, genomics has increased the understanding of many diseases. Proteomics is a rapidly growing research area that encompasses both genetic and environmental factors. The **protein** composition represents the functional status of a biological compartment. The five approaches presented here resulted in the detection of disease-associated **proteins**. Calgranulin B was upregulated in colorectal cancer, and hepatoma-derived aldose reductase-like **protein** was reexpressed in a rat model during hepatocarcinogenesis. In these two investigations, attention was focused on one **protein**, obviously differing in amount, directly after two-dimensional electrophoresis (2-DE). Additional methods, such as enzyme activity measurements and immunohistochemistry, confirmed the disease association of the two candidates resulting from 2-DE subtractive analysis. The following three investigations take advantage of the holistic potential of the 2-DE approach. The comparison of 2-DE patterns from dilated cardiomyopathy patients with those of controls revealed 25 statistically significant intensity differences, from which 12 were identified by amino acid analysis, Edman degradation or matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS). A human myocardial 2-DE **database** was constructed, containing 3300 **protein** spots and 150 identified **protein** species. The number of identified **proteins** was limited by the capacity of our group, rather than by the principle of feasibility. Another field where proteomics proves to be a valuable tool in identifying **proteins** of importance for **diagnosis** is proteome analysis of pathogenic microorganisms such as Borrelia burgdorferi (Lyme disease) and Toxoplasma gondii (toxoplasmosis). Sera from patients with early or late symptoms of Lyme borreliosis contained antibodies of various classes against about 80 antigens each, containing the already described antigens OspA, B and C, flagellin, p83/100, and p39. Similarly, antibody reactivity to seven different marker antigens of T. gondii allowed differentiation between acute and latent toxoplasmosis, an important **diagnostic** tool in both pregnancy and immunosuppressed patients.

L6 ANSWER 12 OF 30 MEDLINE
AN 1999235225 MEDLINE
DN 99235225 PubMed ID: 10219819
TI Role of p53 assessment in management of Barrett's esophagus.
AU Kubba A K; Poole N A; Watson A

CS Department of Surgery, North Manchester General Hospital, University of Manchester, UK.
SO DIGESTIVE DISEASES AND SCIENCES, **(1999 Apr)** 44 (4) 659-67. Ref: 77
Journal code: 7902782. ISSN: 0163-2116.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199905
ED Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990511
AB The risk of developing gastroesophageal adenocarcinoma is increased in patients with Barrett's esophagus. The management of dysplasia in Barrett's esophagus remains controversial. Understanding of the sequence of events preceding malignancy is essential before screening protocols for early **diagnosis** and preventive measures can be implemented. The aim of this review is to examine the published data on the role p53 assessment may play in the management of Barrett's esophagus. Relevant papers were identified by an extensive text word search of the Medline **database** and a review of quoted articles. The p53 abnormality occurs more frequently in highly dysplastic epithelium than in nondysplastic epithelium. However, the retrospective nature of most of the available data could be a significant confounding factor. Our current knowledge suggests that p53 **protein** overexpression does not seem to predict future progression to cancer or determine disease outcome. The p53 abnormality alone can not be reliably used to predict progression of Barrett's esophagus to cancer. We must await long-term evaluation of patients to determine the percentage of patients with p53 gene abnormality, and nondysplastic Barrett's who will progress to dysplasia or carcinoma. Large randomized controlled long-term follow-up studies are much needed.

L6 ANSWER 13 OF 30 MEDLINE
AN 1999150470 MEDLINE
DN 99150470 PubMed ID: 10024692
TI Intermediate filament **proteins** during carcinogenesis and apoptosis (Review).
AU Prasad S; Soldatenkov V A; Srinivasarao G; Dritschilo A
CS Department of Radiation Medicine, Division of Radiation Research, Georgetown University Medical Center, Washington, DC 20007-2197, USA.
NC CA45408 (NCI)
P30-CA51008 (NCI)
SO INTERNATIONAL JOURNAL OF ONCOLOGY, **(1999 Mar)** 14 (3) 563-70.
Ref: 77
Journal code: 9306042. ISSN: 1019-6439.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990506
AB The intermediate filament network spreading from the cell periphery to the nucleus forms dynamic linkages between nuclear matrix, actin microfilaments, and the extracellular matrix. The six different types (types I-VI) of IF **proteins** consisting of nearly 50 different **proteins** form at least nine different kinds of filaments depending on the tissue types: keratins, lamins, vimentin, desmin, neurofilaments,

peripherin, alpha-internexin, glial fibrillary acidic **protein** and nestin. Their tissue specific expression in normal cells and differential expression/assembly in neoplasia has been of immense value in tumor **diagnosis**. At the same time, recent in vitro studies point out that keratins, lamins and vimentin are subject to caspase-mediated proteolysis in an apoptosis-related manner. We reviewed the experimentally demonstrated P4-P1 motif specificities of caspases in the selection of substrates in the IF **protein** family. In addition, we provided clues to possible cleavage of additional IF **proteins** during programmed cell death, based on acceptable cut site motifs indicated by searches using the PIR **protein** sequence **database**. The present review concludes with presentation of evidence on the emerging roles of IFs in association with intermediate filament associated **proteins** in the dynamic remodeling of the cell during development of neoplastic phenotype and execution of apoptosis.

L6 ANSWER 14 OF 30 MEDLINE
AN 2000149625 MEDLINE
DN 20149625 PubMed ID: 10685364
TI HLA genetics for **diagnosis** of susceptibility to early-onset periodontitis.
AU Takashiba S; Ohyama H; Oyaizu K; Kogoe-Kato N; Murayama Y
CS Department of Periodontology and Endodontology, Okayama University Dental School, Japan.
SO JOURNAL OF PERIODONTAL RESEARCH, **(1999 Oct)** 34 (7) 374-8. Ref: 33
Journal code: 0055107. ISSN: 0022-3484.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Dental Journals; Priority Journals
EM 200003
ED Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323
AB Human leukocyte antigens (HLA) are essential in the recognition of foreign antigens in humoral immune response, which is genetically predetermined. Susceptibility to certain diseases that involve the immune response has been studied in relation to distinct HLA types. Although some diseases have been found to correlate to specific HLA loci positively, it has been difficult to isolate HLA types that predispose patients to periodontal destruction. Here, we review the current knowledge and recent advances in HLA genetics and its biology, which determine susceptibility to early-onset periodontitis (EOP). The HLA-DRB1*1501-DQB1*0602 genotype has been found with increasing frequency in EOP patients. This HLA genotype expresses aspartic acid at position 57 and glycine at position 70 on the DQ beta chain, suggesting a capability to bind certain bacterial antigens. The T cell response against the outer membrane **protein** (Ag53) of Porphyromonas gingivalis was examined via this HLA genotype. Strong T cell response against Ag53 p141-161 was inhibited partially by anti-DR antibody, but not by anti-DQ antibody. Possible host and bacterial **peptides** capable of binding DRB1*1501 were elucidated when the **peptide** sequence was compared to gene and **protein** **databases**. These results suggest that patients who have the HLA-DRB1*1501-DQB1*0602 genotype may have an accelerated T cell response to certain periodontopathic bacteria such as P. gingivalis in hyperimmune reactions and thus increased susceptibility to EOP.

L6 ANSWER 15 OF 30 MEDLINE
AN 1999165510 MEDLINE
DN 99165510 PubMed ID: 10068141
TI Proteome analysis. I. Gene products are where the biological action is.
AU Lopez M F

CS ESA Inc., Chelmsford, MA 01824-4171, USA.
SO JOURNAL OF CHROMATOGRAPHY. B, BIOMEDICAL SCIENCES AND APPLICATIONS, **(1999 Feb 5)** 722 (1-2) 191-202. Ref: 94
Journal code: 9714109. ISSN: 1387-2273.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990428
AB Two-dimensional electrophoresis has rapidly become the method of choice for resolving complex mixtures of **proteins**. Since the technique was pioneered in 1975, 2-D gel methods have undergone a series of enhancements to optimize resolution and reproducibility. Recent improvements in the sensitivity of mass spectrometry have allowed the direct identification of polypeptides from 2-D gels by a procedure termed "mass profiling". In combination, these two techniques have made possible the characterization of the complete collection of gene products, or proteome, of an organism. Proteomes are increasingly being documented as interactive informational **databases** available on the World Wide Web (WWW). This availability of organismic global **protein** patterns will no doubt be an invaluable resource aiding the discovery of **diagnostic** and therapeutic disease markers.

L6 ANSWER 16 OF 30 MEDLINE
AN 2000090007 MEDLINE
DN 20090007 PubMed ID: 10626581
TI State-of-the-art for DNA technology in newborn screening.
AU McCabe E R; McCabe L L
CS Mattel Children's Hospital at UCLA, Los Angeles, CA, USA..
emccabe@mednet.ucla.edu
SO ACTA PAEDIATRICA. SUPPLEMENT, **(1999 Dec)** 88 (432) 58-60. Ref: 19
Journal code: 9315043. ISSN: 0803-5326.
CY Norway
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000202
AB Just as metabolites, hormones and **proteins** are measured in newborn screening tests, DNA has become an analyte that is important in the screens for certain disorders. DNA confirmatory testing on the original dried blood specimen reduces the age at **diagnostic** confirmation and antibiotic prophylaxis initiation for neonates with sickle cell disease. Molecular genetic analysis of the initial specimens from newborns with elevated immunoreactive trypsinogen (IRT) for cystic fibrosis (CF) screening permits reduction of the IRT threshold value, improving specificity without compromising sensitivity. Because of this cost reduction, CF neonatal screening programs routinely incorporate DNA confirmatory testing into their initial CF screening algorithm. DNA analysis is also a valuable adjunct in screening programs for congenital adrenal hyperplasia (CAH), improving sensitivity and specificity. Incorporation of DNA into newborn screening programs will continue to be stimulated by development of robust, high throughput technologies for evaluation of this analyte. New paradigms for neonatal screening are evolving, including hearing screening in the newborn nursery. DNA testing,

such as for mutations in the connexin 26 gene, may have a role in the evaluation of those screened positive. Newborn screening dried blood specimens are DNA **databases**. Therefore, there are significant ethical, legal and social issues that must be considered in the storage and utilization of neonatal screening specimens.

L6 ANSWER 17 OF 30 MEDLINE
AN 1998247839 MEDLINE
DN 98247839 PubMed ID: 9588425
TI Natriuretic **peptides**: physiology, therapeutic potential, and risk stratification in ischemic heart disease.
AU Stein B C; Levin R I
CS Cardiology Section, New York University Medical Center, NY 10016, USA.
SO AMERICAN HEART JOURNAL, **(1998 May)** 135 (5 Pt 1) 914-23. Ref: 73
Journal code: 0370465. ISSN: 0002-8703.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199805
ED Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980519
AB BACKGROUND: The natriuretic **peptide** family consists of four molecules that share significant amino acid sequence homologic characteristics and a looped motif. Atrial natriuretic **peptide** and brain natriuretic **peptide** are similar in their ability to promote natriuresis and diuresis, inhibit the renin-angiotensin-aldosterone axis, and act as vasodilators. Understanding of the actions of C-type natriuretic **peptide** and dendroaspis natriuretic **peptide** is incomplete, but these two new family members also act as vasodilators. Because of the rapid evolution of information about this **peptide** family, we reviewed the state of the art with respect to risk stratification and therapeutic ability. METHODS: English-language papers were identified by a MEDLINE **database** search covering 1966 through 1997 and supplemented with bibliographic references and texts. CONCLUSIONS: The natriuretic **peptides** are counterregulatory hormones with prognostically important levels. They are similarly upregulated in heart failure and counteract neurohormones that induce vasoconstriction and fluid retention. BNP may be the superior prognosticator for risk stratification after myocardial infarction and is independent of left ventricular ejection fraction. Lastly, experimental trials suggest that administration of exogenous natriuretic **peptides** or inhibitors of their catabolism to patients with ischemic heart disease may be clinically beneficial.

L6 ANSWER 18 OF 30 MEDLINE
AN 1998375650 MEDLINE
DN 98375650 PubMed ID: 9709885
TI Cytomegalovirus polyradiculopathy in patients with AIDS.
AU Anders H J; Goebel F D
CS Medizinische Poliklinik, Ludwig-Maximilian University, Munich, Germany.
SO CLINICAL INFECTIOUS DISEASES, **(1998 Aug)** 27 (2) 345-52. Ref: 100
Journal code: 9203213. ISSN: 1058-4838.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals; AIDS
EM 199810
ED Entered STN: 19990106

Last Updated on STN: 20000303
Entered Medline: 19981027

AB Using the MEDLINE **database**, we evaluated 103 cases of AIDS-related cytomegalovirus (CMV) polyradiculopathy (PRP). In 13% of cases, PRP was the initial manifestation of AIDS. Hyporeflexia was present in 100% of cases; lower limb weakness, in 100%; urinary retention, in 94%; paresthesia, in 79%; sensory loss, in 80%; and a Babinski's sign, in 16%. Mean cerebrospinal fluid (CSF) parameters +/- SD were as follows: white blood cell count, 651 +/- 1,053 x 10(6)/L; **protein** level, 2.28 +/- 1.78 g/L; and CSF/serum glucose ratio, 0.48 +/- 0.17. Gadolinium enhancement of meninges on a magnetic resonance image and abnormalities on a myelogram were noted in 31% and 17% of cases, respectively. Mean survival time +/- SD was 5.4 +/- 1.8 weeks for untreated patients and 14.6 +/- 9.4 weeks for patients treated with ganciclovir ($P < .0001$), but it was only 7.2 +/- 3.0 weeks for patients receiving ganciclovir treatment at the onset of PRP. CMV-related PRP is an uncommon but distinctive complication of AIDS. Early **diagnosis** is possible, and other causes can be excluded by lumbar magnetic resonance imaging and by the presence of typical CSF changes, as shown by polymerase chain reaction of CMV. Retrospectively, survival time for naive patients was increased by ganciclovir therapy and may even be underestimated in this evaluation of historical reports.

L6 ANSWER 19 OF 30 MEDLINE
AN 1998120264 MEDLINE
DN 98120264 PubMed ID: 9458681
TI HIV-associated nephropathy.
AU Winston J; Klotman P E
CS Mount Sinai School of Medicine, New York, NY 10029, USA.
NC M01 RR00071 (NCRR)
SO MOUNT SINAI JOURNAL OF MEDICINE, **(1998 Jan)** 65 (1) 27-32. Ref: 49
Journal code: 0241032. ISSN: 0027-2507.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 199803
ED Entered STN: 19980312
Last Updated on STN: 19980312
Entered Medline: 19980305

AB BACKGROUND: Patients with HIV-1 infection are at risk for developing renal diseases with diverse etiologies. Acute renal failure occurs in up to 20% of hospitalized patients with HIV infection, and chronic renal disease of diverse etiology has been reported. The single most common cause of chronic renal insufficiency in HIV-1+ patients is HIV-associated nephropathy (HIVAN). Typical morphologic features include enlarged kidneys, microcystic tubule dilatation, tubulointerstitial inflammation, and focal and segmental glomerulosclerosis. METHODS: The pathogenesis, epidemiology, and treatment options for HIVAN are discussed. In studying the epidemiology of the disease, we reviewed several renal disease **databases**, including the United States Renal Data Systems and New York State End Stage Renal Disease Network. We have previously reported our experience with HIVAN at Mount Sinai Medical Center. RESULTS: The exact cause of the renal disease remains unknown. The importance of a direct effect of HIV-1 viral **protein**(s) or renal HIV-1 gene expression in disease pathogenesis is supported in the murine model of HIVAN, but definitive proof of renal cell infection in humans is lacking. Further study is required to clarify this issue. We estimate that HIVAN is the fourth leading cause of end-stage renal disease (ESRD) among Blacks between the ages of 20 and 64 years, only slightly behind hypertension, diabetes, and chronic glomerulonephritis. At Mount Sinai Hospital HIVAN accounts for 20% of newly **diagnosed** ESRD in young black adults.

It has become the third leading cause of ESRD in this group, after hypertension and diabetes. CONCLUSIONS: In seropositive patients with renal disease, renal biopsies should be performed to confirm the **diagnosis** and determine the true incidence. Special attention should be directed toward understanding the underlying cause(s) of HIVAN. A multicenter trial to explore the potential for antiviral therapy in this disease should be initiated.

L6 ANSWER 20 OF 30 MEDLINE
AN 97472450 MEDLINE
DN 97472450 PubMed ID: 9328462
TI Mammalian telomerase: catalytic subunit and knockout mice.
AU Kipling D
CS Department of Pathology, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK.. kiplingd@cardiff.ac.uk
SO HUMAN MOLECULAR GENETICS, **(1997 Nov)** 6 (12) 1999-2004. Ref: 43
Journal code: 9208958. ISSN: 0964-6906.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971219
AB For the second time this year random cDNA sequencing, in combination with data from unicellular eukaryotes, has made a significant contribution to the analysis of human telomerase. Two groups have reported mammalian homologues of the Tetrahymena p80 telomerase-associated **protein**, in both cases the key breakthrough being mammalian cDNA clones with **database** matches to Tetrahymena p80. This has now been joined by the sequence of a candidate for the human telomerase catalytic subunit. The discovery that its message abundance closely follows telomerase activity could make a major impact on the utility of telomerase as a **diagnostic** marker for human malignancy. In addition, Blasco et al . report the phenotype of a transgenic mouse deleted for the mTR gene, which encodes the essential RNA component of telomerase. Interestingly tumour formation is unaffected in these mice, strengthening the argument that telomerase expression in mouse tumourigenesis is an innocent bystander rather than a necessary event. However, fundamental differences between the genomic organisation of mouse and human telomeres mean that the mouse is not a straightforward model to critically test the role of telomere loss and telomerase in human malignancy.

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for a good recovery, whereas no effect was observed from protease inhibitors. No detectable loss was observed in the lyophilized product. In a subsequent experiment, the stability of alb-OC was analyzed under optimal conditions for prolonged periods of time. Storage conditions for the diluted product were as follows: alb-OC concentration, 375 mg/L in PBS containing 4% (w/v) ovalbumin; 0.1% (w/v) kathon; sealed plastic tubes. The lyophilized product was prepared from the same solution and was analyzed for up to 4 weeks at 37°C. The data are given in Fig. 2 and demonstrate that at 4°C alb-OC was stable for at least 1 month. At higher temperatures, substantial losses were observed after a few days. The lyophilized product was stable at 37°C for at least 1 month.

In this paper, we demonstrate that peptides linked to a carrier protein may be used as a calibrator in enzyme assays for biomarkers. The method was validated with the bone Gla-protein osteocalcin, but may be used in a wide variety of comparable applications. In the case of alb-OC, the chimeric molecule mimicked the immunochemical properties of osteocalcin but was more than 10 times larger than the native molecule. The preparation procedure for albumin-linked peptides is simple and reproducible, and may be further improved by more rigid standardization or automated procedures. The stability of lyophilized material at temperatures up to 37°C and that of soluble material at 4°C were satisfactory; at higher temperatures, soluble alb-OC degraded with a biphasic curve, leading to a loss of approximately 50% after 4 weeks. If required, the stability may be improved, e.g., by sterile filtration of the solvent or by adding protease inhibitor cocktails (3). We conclude that albumin-linked peptides form a good alternative in cases in which the authentic protein cannot be used as a reference material in test kits, for instance because it is expensive, difficult to obtain, unstable, poorly soluble in saline, or associated with infection risks.

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2. Rosenquist, C., Qvist, P., Bjarnason, N., and Christiansen, C. (1995) Measurement of a more stable region of osteocalcin in serum ELISA with two monoclonal antibodies. *Clin. Chem.* **41,** 1439–1445.
3. Baumgrass, R., Daenzer, M., and Felsenberg, D. (1999) Improved *in vitro* stability of serum by using a new commercially available antiproteolytic compound. *Clin. Chim. Acta* **28,** 47–55.

Desalting of In-Gel-Digested Protein Sample with Mini-C18 Columns for Matrix-Assisted Laser Desorption Ionization Time of Flight Peptide Mass Fingerprinting[1]

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Received May 9, 2000

Mass spectrometry based techniques such as MALDI-ToF[3] peptide mass fingerprinting (1) and nanoelectrospray Q-ToF *de novo* sequencing (2) have now become the methods of choice for protein identification. In recent years, many "in-gel" protein digestion and peptide extraction methods have been reported (3–5); however, little mention has been made of simple sample cleanup/desalting techniques that we find are equally important for confident identification of proteins. The general consensus from the literature appears to be that sample cleanup/desalting is not necessary for MALDI-ToF-based methods of protein identification. We report here a quick cleanup method using commercially available mini-C18 columns (ZipTips, Millipore) and demonstrate a great improvement in the signal-to-noise ratio of peptide mass maps obtained from MALDI-ToF after its use, thus making peptide mass fingerprinting more reliable as a first method of identification. This cleanup method also renders the peptide sample suitable for *de novo* sequencing of peptides using nanoelectrospray MS/MS with the Q-ToF mass spectrometer (MicroMass).

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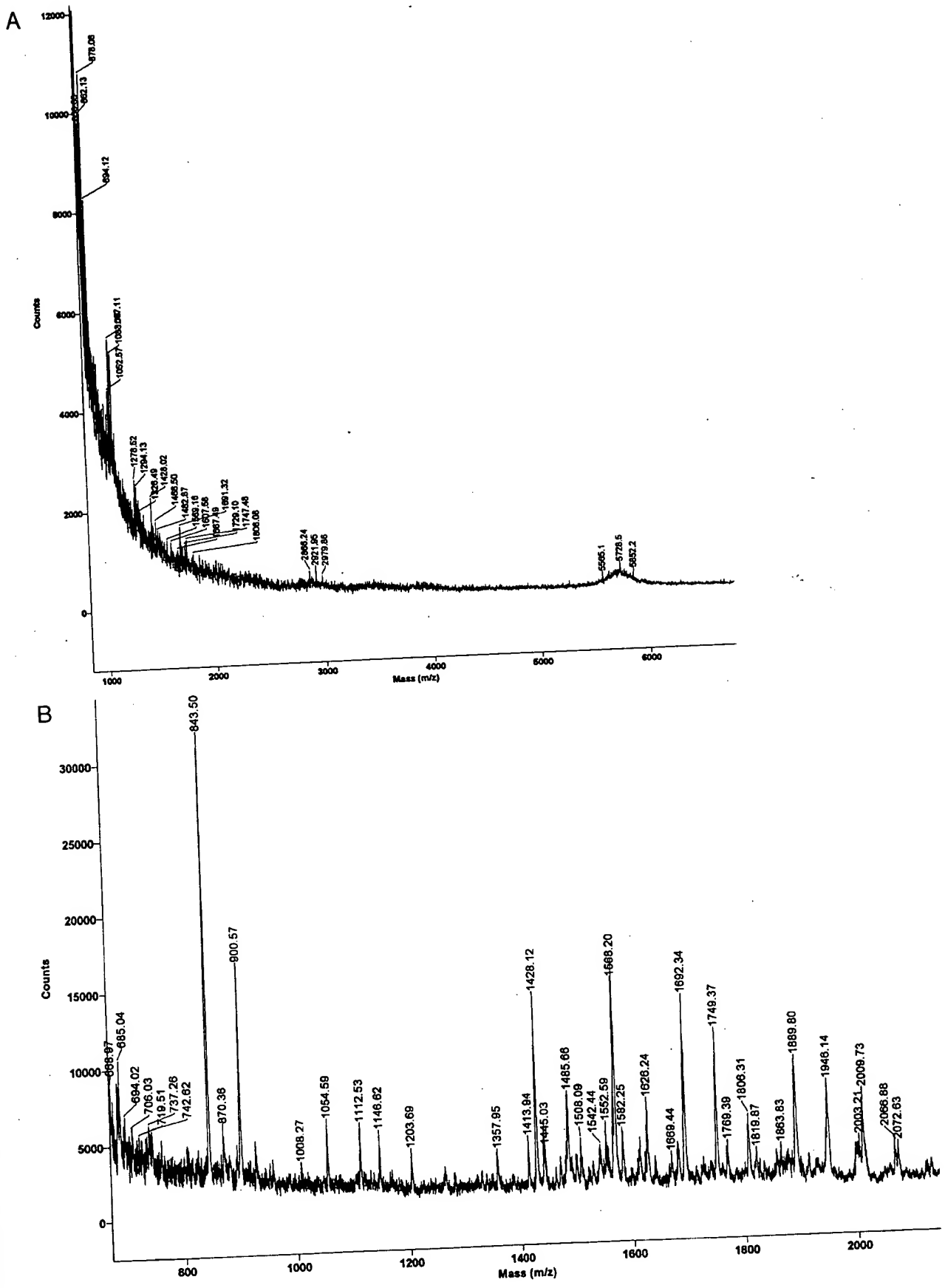
[2] To whom correspondence should be addressed. Fax: (416) 813-8700. E-mail: r.bagshaw@utoronto.ca.

[3] Abbreviations used: MALDI-ToF, matrix-assisted laser desorption ionization time of flight; Q-ToF, quadrupole time of flight; IEF, isoelectrofocusing.

FIG. 1. MALDI-TOF peptide mass maps of an in-gel peptide digest (A) before and (B) after desalting with ZipTips. Three picomoles (~300 ng) of phosphorylase *b* was run on a 1D SDS–PAGE, stained with Coomassie blue, excised, digested in-gel with trypsin, extracted, and in (B) desalted with C18 ZipTips (Millipore). One microliter of each sample (5-μL total volume in each case) was used to obtain the mass spectra. Note the abscissa is much larger in B.

Analytical Biochemistry **284,** 432–435 (2000)
doi:10.1006/abio.2000.4718
0003-2697/00 $35.00


A
Counts
Mass (m/z)
694.12
B
Counts
Mass (m/z)
843.50
800.57
685.04
706.03
719.51
737.26
742.82
870.36
1054.59
1112.53
1146.62
1203.69
1357.95
1413.84
1428.12
1445.03
1485.66
1508.09
1542.44
1552.59
1582.25
1626.24
1668.20
1692.34
1749.37
1768.39
1806.31
1818.87
1863.83
1889.80
1946.14
2003.21
2009.73
2066.88
2072.63

To demonstrate the need for sample cleanup/desalting, a standard protein, phosphorylase *b* (Pharmacia), was separated by 1D SDS–PAGE. However, we have used this method with equal success for proteins separated by 2D IEF/SDS–PAGE (data not shown). The gel was subsequently stained with 0.1% Coomassie blue in 50% methanol/10% acetic acid. Destaining was with several changes of 15% methanol/10% acetic acid. The protein spot or band was excised neatly using a clean scalpel blade and placed in a 2-mL siliconized microfuge-style tube. For protein digestion and peptide extraction, many procedures that differ slightly exist in the literature. We developed a protocol that combines the putative advantages from several methods. First, the gel piece was washed and completely destained by four or five 15-min, 1-mL washings with a 30 mM ammonium bicarbonate/40% acetonitrile solution and gentle shaking on a rotary platform (bands of great intensity took somewhat longer to destain). The wash solutions were removed by aspiration. After the final wash, the gel piece was crushed lightly on the bottom of the tube by using the plunger from a 1-mL slip-tip latex-free syringe (Becton–Dickinson). The lack of rigidity in the rubber bulb of the plunger and the broad cone-shaped bottom of the 2-mL microtube allow for the generation of gel pieces that are small enough to allow for efficient protein digestion and peptide extraction but large enough to not impede subsequent desalting. The gel was then dried down in a SpeedVac concentrator (Savant). Modified sequencing-grade trypsin (Promega), supplied as a lyophilized powder in 20-μg aliquots, was dissolved to 0.2 μg/μL with the accompanying resuspension buffer and was warmed at 30°C for 15 min as per the manufacturer's suggested directions. The mass of dried gel was transferred to a 0.2-mL tube suitable for use with the GeneAmp 2400 PCR system (Perkin Elmer) equipped with a hottop assembly. The gel mass was then rehydrated with 3 μL (0.6 μg) of trypsin solution and 30–50 μL of a 50 mM ammonium bicarbonate/1 mM $CaCl_2$ solution. The tube was allowed to sit on ice for 1 h before being transferred to 37°C on the GeneAmp. Additional 50 mM ammonium bicarbonate was added if the gel had soaked up all the rehydration solution. Digestion proceeded for 18 h. After digestion, the supernatant liquid was removed and placed in a siliconized 0.5-mL microfuge tube. The gel was then treated with 30–50 μL of the following solutions: 50 mM ammonium bicarbonate (1×), 50% acetonitrile/1% trifluoroacetic acid (TFA) (2×), 20% formic acid/15% 2-propanol/25% acetonitrile (1×), and 80% acetonitrile (1×). Following the addition of each solution, the tube was vortexed for 20 s, centrifuged briefly, and allowed to sit at room temperature for 10 min before the supernatant was removed and pooled with the rest of the extracted material in the 0.5-mL siliconized tube. The pooled fractions were dried completely in a SpeedVac concentrator.

At this point, the material can be redissolved in a small amount of 50% acetonitrile/1% TFA and submitted for MALDI-ToF. However, the following desalting step with C18 ZipTips (Millipore) produces far superior results. The dry extracted material was redissolved and allowed to sit for 10 min at room temperature in 20 μL of sample preparation solution (0.8 M guanidine/2.5% TFA). The prewetting, equilibration, binding of sample, washing, and elution of bound material with the ZipTip were conducted as suggested in the manufacturer's directions, with the following exceptions. The prewetting step was carried through for at least 2 min of multiple (>20) aspiration/dispensing cycles to thoroughly remove air bubbles from the column material. In addition, it is critical to not introduce air into the column bed during the subsequent procedures. Thus before changing solutions between steps, the liquid was dispensed from the tip such that the meniscus remained slightly above the top of the column bed. The bound and washed peptides on the column were eluted into a 0.5-mL siliconized microfuge tube containing 5 μL of 50% acetonitrile/0.1% acetic acid and stored upright at −20°C.

Obtaining a peptide mass map from MALDI-ToF requires <1 μL of desalted sample. To prevent contamination and losses from sample handling, the entire sample was provided to the mass spectroscopy facility to perform MS on MALDI-ToF, and remaining sample was retrieved for future analysis. Figure 1 shows the MALDI peptide mass map of an "in-gel-digested" protein before desalting and after desalting. About 300 ng (~3 pmol) of phosphorylase *b* (Pharmacia) was separated by SDS–PAGE and stained as above, resulting in a faint blue band. The "after" spectrum (Fig. 1B) clearly has more peptide species represented. The overall signal is also greatly enhanced after desalting as shown by the absence of the concave baseline below *m/z* 2000 seen in the "before" spectrum (Fig. 1A). Peptide mass fingerprinting was performed by inputting peptide masses from the peptide mass map with *m/z* ratios between 700 and 2100 into the program MS-Fit (ProteinProspector, UCSF, http://prospector.ucsf.edu). The search was conducted on the NCBI-nr database with a mammalian species limitation and a ±0.5-Da peptide mass tolerance (results not shown). Identification of the protein as phosphorylase was only apparent for the desalted sample, having a reasonably high MOWSE score (2.12e + 004, 23% of peptides matching) as well as having similar proteins identified by database "hits" in the first few results. The undesalted sample produced results typical of a poor-quality sample: very few matched peptide masses from the database and a very low MOWSE score (not shown). Thus without cleanup/desalting, an inaccurate and unreliable identification was all that could be obtained from the MALDI data (Fig. 1A). This example clearly shows that desalting and sample cleanup with ZipTips can dra-

matically improve the signal-to-noise ratio of in-gel peptide digests and can provide positive results from samples that seemingly lack any peptides.

Obtaining a peptide mass map from MALDI-ToF and performing peptide mass fingerprinting constitute an inexpensive, yet essential, first step for protein identification. The data it provides may or may not be sufficient to identify the protein contained in the gel piece. If identification cannot be made, the overall quality of the peptide mass map is directly related to the quality of both the original protein sample and the subsequent digestion and purification procedures applied to it. Thus the MALDI-ToF data can be used to predict the degree of success that could be achieved if the remaining sample were analyzed by more expensive and time-consuming identification methods such as sequence tagging and *de novo* sequencing using nanoelectrospray MS/MS.

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A Transient Assay Reveals That Cultured Human Cells Can Accommodate Multiple LINE-1 Retrotransposition Events

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Long interspersed nuclear elements (LINEs or L1s)[2] are retrotransposons in the human genome, which compose about 17% of nuclear DNA (1). The vast majority of L1s cannot retrotranspose because they are 5′ truncated, internally rearranged, or mutated. However, an estimated 60 human L1s remain retrotransposition competent (RC-L1s) (2).

RC-L1s originally were isolated as the progenitors of mutagenic insertions into the Factor VIII and dystrophin genes (3, 4). These L1s are 6.0 kb in length and contain a 5′ untranslated region (UTR) harboring an internal promoter, two nonoverlapping open-reading frames (ORF1 and ORF2), and a 3′ UTR ending in a poly(A) tail. ORF1 encodes a 40-kDa RNA-binding protein (p40) (5, 6), whereas ORF2 encodes endonuclease and reverse transcriptase (RT) activities (7, 8). In addition, L1s usually are flanked by variable-length target site duplications, which are hallmarks of the retrotransposition process (9).

We recently developed a genetic assay to study L1 retrotransposition in cultured human cells (10). Candidate L1s were tagged with a selectable marker (*mneoI*) that could be activated upon retrotransposition to confer resistance to the drug G418 ($G418^R$) (11). Using this assay, we identified numerous RC-L1s in both human and mouse genomes and demonstrated that the ORF1- and ORF2-encoded proteins are essential for retrotransposition (2, 10, 12). However, the above assay has some limitations because it requires 40 days to complete, involves the serial transfer of cells to different tissue culture flasks, and is best conducted in cell lines that replicate the pCEP4 expression vector efficiently.

To overcome some of the above limitations, we developed a rapid, quantitative transient L1 retrotransposition assay (Fig. 1). We first modified our original transfection protocol in the following manner: (1) we used the FuGene 6 nonliposomal transfection reagent (Roche Biochemicals); and (2) we stored Qiagen-prepared plasmid DNA preparations in 30-μl aliquots (usually containing between 10 and 20 μg DNA/aliquot) at −20°C. The FuGene 6 reagent allowed us to perform transfections in serum-containing medium and resulted in low cell cytotoxicity. Storing the plasmid DNA in small aliquots limited the freeze/thaw cycles of the samples, leading to decreased experimental variability (not shown). Plasmid DNAs were checked for superhelicity by electrophoresis on 0.7% agarose/ethidium bromide gels and only highly supercoiled preparations of DNA (>90%) were used for transfections.

In a typical experiment, we plated 2×10^5 HeLa cells in each well of a 6-well tissue culture dish. The following day, duplicate dishes were cotransfected with equal

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[2] Abbreviations used: LINEs or L1s, long interspersed nuclear elements; RC-L1s, retrotransposition-competent L1s; UTR, untranslated region; ORF, open-reading frame.

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